(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 816 378 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
07.01.1998 Bulletin 1998/02

(51) Int Cl.[6]: C07K 9/00, A61K 38/14

(21) Application number: 97304495.1

(22) Date of filing: 25.06.1997

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
RO

(30) Priority: 28.06.1996 US 20774 P
01.05.1997 US 847069

(71) Applicant: ELI LILLY AND COMPANY
Indianapolis, Indiana 46285 (US)

(72) Inventors:
- Cooper, Robin David Grey
Indianapolis, Indiana 46220 (US)
- Rodriguez, Michael John
Indianapolis, Indiana 46260 (US)
- Snyder, Nancy June
Charlottesville, Indiana 46117 (US)
- Zweifel, Mark James
Indianapolis, Indiana 46214 (US)

(74) Representative: Hudson, Christopher Mark et al
Lilly Industries Limited
European Patent Operations
Erl Wood Manor
Windlesham Surrey GU20 6PH (GB)

(54) Glycopeptide antibiotic amide derivatives

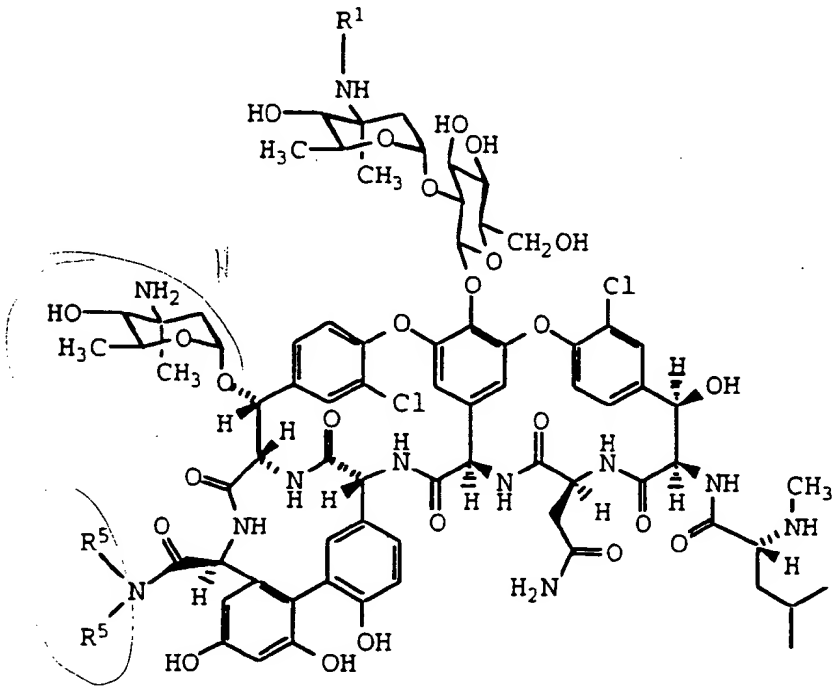
(57) The present invention is directed to amides of antibiotic A82846B (also known as chloroorienticin A), and of N^4-derivatives of A82846B. The present amide compounds are useful as antibacterials, especially for the control of gram positive bacteria; the compounds are particularly useful for the control of resistant bacterial strains, such as vancomycin-resistant-enterococci ("VRE").

EP 0 816 378 A1

Description

The present invention is directed to glycopeptide amides, more particularly to amides of antibiotic A82846B, also known as chloroorienticin A, and of N^4-derivatives of A82846B. These amides are useful as antibacterials, especially for the control of gram positive bacteria; the compounds are particularly useful for the control of resistant bacterial strains, such as vancomycin-resistant-enterococci ("VRE").

The compounds of the present invention are defined by Formula I:



I

wherein R^1 is:

hydrogen or $-CH_2R^2$;

wherein R^2 is:

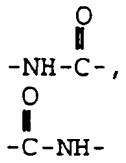
hydrogen,
alkyl of C_1-C_{15},
alkenyl of C_2-C_{15},
alkynyl of C_2-C_{15},
haloalkyl of C_1-C_7,
acenaphthenyl,
2-fluorenyl,
9,10-dihydro-2-phenanthrenyl,
R^3,
alkyl of C_1-C_{11}-R^3,
alkenyl of C_2-C_7-R^3,
alkynyl of C_2-C_7-R^3, or
alkyl of C_1-C_7-O-R^3,

wherein R^3 is a radical of the formula:

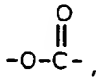
$$-R_4-\left[\text{linker}_{(0 \text{ or } 1)}-R^4\right]_{(0 \text{ or } 1)}$$

wherein each R^4 independently represents phenyl, cycloalkyl of C_5-C_6, naphthyl, or thienyl, each of which is unsubstituted or is optionally substituted with one or two substituents, each of which is independently alkyl of C_1-C_{10}, haloalkyl of C_1-C_2, haloalkoxy of C_1-C_2, alkoxy of C_1-C_{10}, halo, cyano, or nitro;
and "linker" is:

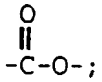
- alkylene of C_1-C_3,
- O-alkylene of C_1-C_6,
- alkylene of C_1-C_6-O-,
- O-,
- N(H or loweralkyl of C_1-C_3)-,
- S-,
- SO-,
- SO_2-,



- CH=CH-,
- C≡C-,
- N=N-,



or

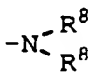


and wherein R^5 is defined as follows:

(1) each R^5 independently represents hydrogen,

cycloalkyl of C_5-C_6.
cycloalkenyl of C_5-C_6,
phenyl or substituted phenyl bearing from one to three substituents, each of which is independently
halo,
nitro,
loweralkyl of C_1-C_4,
cycloalkyl of C_5-C_6,
loweralkoxy of C_1-C_4,
haloloweralkyl of C_1-C_4, or haloloweralkoxy of C_1-C_4;
naphthyl,

biphenylyl,
radical of the formula $-R^6-(R^7)0$, 1, or 2, wherein R^6 is loweralkyl of C_1-C_8 optionally substituted by from one to three substituents, each of which is independently selected from the group consisting of halo, nitro, cyano, loweralkoxy of C_1-C_4, haloloweralkyl of C_1-C_4, and haloloweralkoxy of C_1-C_4; and R^7 is



wherein each R^8 is independently hydrogen or loweralkyl of C_1-C_4 or one R^8 is hydrogen and the other R^8 is tert-butoxycarbonyl, or R^7 is phenyl or substituted phenyl as defined above, or
(2) one R^5 is hydrogen and the other R^5 is (2-furanon-3-yl); or
(3) both R^5s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C_1-C_2, loweralkoxy of C_1-C_2, phenyl, benzyl, or C_1-C_6-alkanoyl; or a salt thereof.

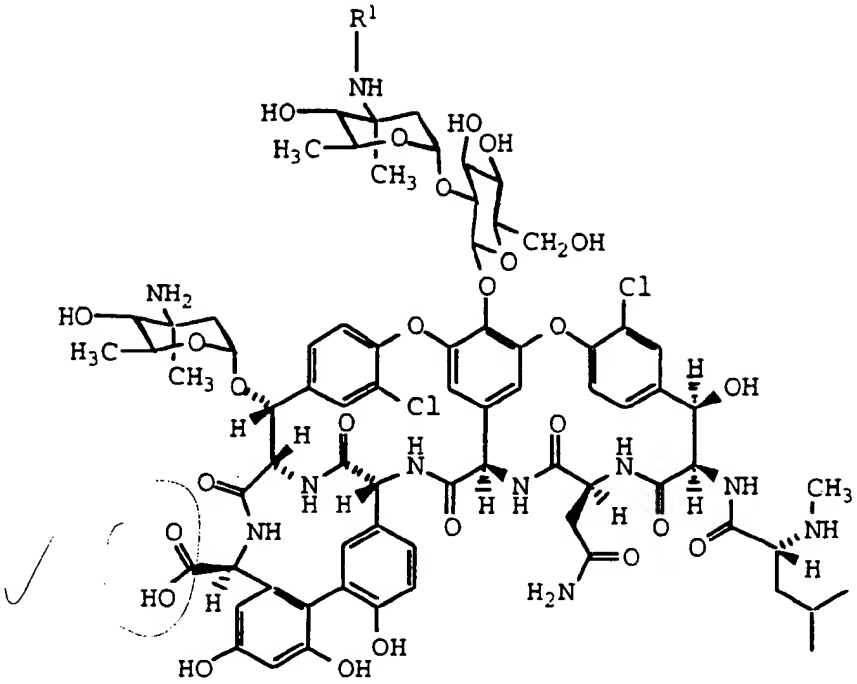
Certain compounds of the present invention are preferred. Amides of A82846B derivatives (R^1=-CH_2R^2) generally exhibit antibacterial activity at concentrations lower than the amides of A82846B itself (R^1=H).

Antibacterial activity is further enhanced by employing certain "-CH_2R^2" groups such as the following:

(4-phenylbenzyl)
(4-(4-chlorophenyl)benzyl)
(4-(4-methylphenyl)benzyl)
(4-phenoxybenzyl)
((4-n-butylphenyl)benzyl)
(4-benzylbenzyl)

Primary amines (H_2N-R_5) may sometimes be preferred, for availability of starting materials and convenience of synthesis. Compounds wherein R^2=R^3 are also preferred. Other preferences will be apparent from the further teachings herein.

The compounds of the present invention are prepared by reacting A82846B (R^1=hydrogen) or an N^4-derivative thereof (R^1=-CH_2R^2), defined by Formula II:



II

with an amine of the formula

The Formula II compounds are known or prepared in standard procedures. A82846B (R^1=hydrogen) is the subject of U.S. Patent 5,312,738. The derivatives, those compounds of Formula II wherein R^1 is $-CH_2R^2$, are prepared from A82846B by reductive alkylation. A82846B is initially reacted with an aldehyde to form an intermediate Schiff's base, which is subsequently reduced to obtain the desired Formula II compound. Alkylation at the N^4 position, in preference to other reactive sites in the molecule, is favored by supplying a source of soluble copper. Copper (II) acetate is a preferred source of copper. The copper is preferably supplied in an amount equimolar with the A82846B. Examples of the Formula II compounds are to be found in EPO 667,353, published August 16, 1995.

The reaction of Formula II compounds and amines of the formula

yields the compounds of the present invention. The reaction conditions are not critical. The reaction proceeds well when carried out in a solvent such as DMF, DMSO, or a mixture of DMF and DMSO, and at reaction temperatures of 0 to 100_C, although the reaction is conveniently conducted at room temperature. Generally, the reaction is conducted with equimolar proportions of the reactants or an excess of the amine.

The reaction is facilitated by the use of a coupling agent, such as:

a) benzotriazol-l-yloxy-tripyrrolidinophosphonium hexafluorophosphate, one form of which is sold under the trademark PyBOP® (Calbiochem-Novabiochem AG);
b) benzotriazol-l-yloxytris(dimethylamino)phosphonium hexafluorophosphate ("BOP");
c) 0-benzotriazol-1-yl-N,N,N'N'-tetramethyluronium hexafluorophosphate ("HBTU");
d) 1,3-dicyclohexylcarbodiimide ("DCC"), alone or in combination with l-hydroxybenzotriazole hydrate ("HOBT");
e) N,N'-dicyclohexyl-4-morpholinecarboxamidine ("WSC") ; and
f) (2-ethoxy-1-ethoxycarbonyl)-1,2-dihydroquinoline ("EEDQ").

The first listed of these is preferred. In general, the coupling agent is supplied in an equimolar amount or in an excess.

The product can be isolated by precipitation or by lyophilization of the reaction mixture, and purified if desired in a conventional manner, such as by HPLC. Characterization of products is best accomplished by Fast Atom Bombardment Mass Spectroscopy (FAB•MS).

When it is desired to employ a salt, a compound of the present invention can be reacted with a mineral or organic acid, in techniques well known to those skilled in the art. Pharmaceutically-acceptable salts are preferred.

The following example reports the preparation of an exemplary compound of the present invention.

Example 1:

N^4-(4-PHENOXYBENZYL)A82846B, 3-(DIMETHYLAMINO)PROPYLAMIDE, TRIFLUOROACETATE SALT

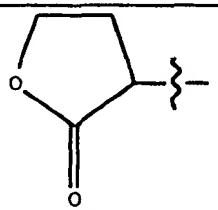
A mixture of N^4-(4-phenoxybenzyl)A82846B, trifluoroacetate salt, (0.668 g, 0.376 mmol, 1.0 equivalent) in 25 ml dimethylsulfoxide (DMSO) under an atmosphere of argon was treated with 3-(dimethylamino)propylamine (0.038 g, 0.376 mmol, 1.0 eq.) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP®) (0.196 g, 0.376 mmol, 1.0 eq). The mixture was stirred at room temperature for 1 hour, diluted with 100 ml H_2O, and lyophilized to give a solid.

The analytical method for analysis was 15% CH_3CN/0.1% TFA at time 0 to 80% CH_3CN/0.1% TFA at 15 minutes. The UV wavelength used was 235 nm and the flow rate 2 ml/minute. Analysis was done using a Waters Nova-pak C18 RCM column (8 x 100 mm) with a Nova-pak C18 guard insert. The solid was purified by preparative reverse-phase high performance liquid chromatography (HPLC) using a Waters 3 x (40 x 100 mm) C18 Nova-pak cartridge with Waters C18 Nova-pak guard insert and utilizing a TFA buffer system. The desired fraction was lyophilized to give the trifluoroacetate salt, a white solid (0.455 g, 55%). The product was characterized by FAB•MS, (M+3H), 1860.

Other products of the present invention were prepared as in Example 1 or with some modifications of the procedure. Modifications included varying the solvent, providing a longer reaction time, up to 123 hours, increasing the amount of amine and/or coupling agent up to 5 equivalents, and using the compound of Formula I as a free base. The reaction appeared to work best with DMSO, but DMF was easier to remove. The reaction was analyzed by HPLC to determine if product was present; if the reaction was incomplete, more amine (1-5 eq) and coupling agent (1-5 eq) were added with solvent and the reaction was continued from 3.5 hours to 48 hours longer.

Other examples of the present invention are listed in Table 1.

TABLE I

Ex. No.	R^5	R^1	Name	Yield	Mass Spec. FAB-MS (M+3H)
2	CH_3-	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, methylamide, trifluoroacetate salt	52	1773
3	n-C_4H_9-	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, n-butylamide, trifluoroacetate salt	19	1814
4	$(CH_3)_3$-C-	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, tert-butylamide, trifluoroacetate salt	38	1814
5	$(CH_3)_3$-C-	4-phenoxybenzyl	N^4-(4-phenoxybenzyl)A82846B, tert-butylamide, trifluoroacetate salt	8.5	1831
6	n-C_8H_{17}-	4-phenoxybenzyl	N^4-(4-phenoxybenzyl)A82846B, n-octylamide, trifluoroacetate salt	27	1885
7	DL 	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, DL-(2-furanon-3-yl)amide	20	1841
8	4-cyclohexylphenyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, (4-cyclohexylphenyl)amide, trifluoroacetate salt	8	1915

EP 0 816 378 A1

9	benzyl	4-phenoxybenzyl	N^4-(4-phenoxybenzyl)A82846B, benzylamide, trifluoroacetate salt	30	1864
10	benzyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, benzylamide	47	1849

11	benzyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, benzylamide, HCl salt		
12	4-methoxybenzyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, (4-methoxybenzyl)amide, trifluoroacetate salt	43	1878
13	3-methoxypropyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, (3-methoxypropyl)amide	N.D.	1830
14	phenethyl	4-phenoxybenzyl	N^4-(4-phenoxybenzyl)A82846B, phenethylamide, trifluoroacetate salt	27	1880
15	phenethyl	(4-n-butylbenzyl)	N^4-(4-n-butylbenzyl)A82846B, phenethylamide, trifluoroacetate salt	N.D.	1842
16	phenethyl	hydrogen	A82846B, phenethylamide, trifluoroacetate salt	27	1696
17	phenethyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, phenethylamide	58	1862
18	phenethyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, phenethylamide, HCl salt	37	1862
19	phenethyl	4-(4-methylphenyl)-benzyl	N^4-(4-(4-methylphenyl)benzyl)-A82846B, phenethylamide	15	1875
20	3-phenyl-n-propyl	hydrogen	A82846B, (3-phenyl-n-propyl)amide	N.D.	1710
21	$(CH_3)_2N-CH_2-CH_2-CH_2-$	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, (3-(dimethylamino)-n-propyl)amide	26	1844

22	3,3-diphenyl-n-propyl	4-phenylbenzyl	N^4-(4-phenylbenzyl)A82846B, (3,3-diphenyl-n-propyl)amide	16	1953
23	$(CH_3)_2N-CH_2-CH_2-CH_2-$	hydrogen	A82846B, (3-(dimethylamino)-n-propyl)amide, trifluoroacetate salt	19	1678
24	benzyl	hydrogen	A82846B, benzylamide, trifluoroacetate salt	48	1682
25	5-(tert-butoxycarbonylamino)-pentyl	4-(4-chlorophenyl)-benzyl	N^4-(4-(4-chlorophenyl)benzyl)-A82846B, 5-(tert-butoxycarbonylamino)-pentylamide, tris(trifluoroacetate) salt	21	1976
26	5-aminopentyl	4-(4-chlorophenyl)-benzyl	N^4-(4-(4-chlorophenyl)benzyl)A82846B, 5-aminopentylamide, tetra(trifluoroacetate) salt	61	1878

The invention is further illustrated by Examples 25 and 26.

Example 25:

N^4-(4-(4-CHLOROPHENYL)BENZYL)A82846B, 5-(TERT-BUTOXYCARBONYLAMINO)PENTYLAMIDE, TRIS (TRIFLUOROACETATE) SALT

A mixture of N^4-(4-(4-chlorophenyl)benzyl)A82846B, diphosphate salt (0.5 g, 0.251 mmol, 1.0 equivalent) in 8 ml dimethylformamide (DMF) and 4 ml dimethylsulfoxide (DMSO) under an atmosphere of nitrogen was treated with benzotriazol-l-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBop®) (0.261 g, 0.502 mmol, 2.0 eq), N,N-diisopropylethylamine (0.097 g, 131 µl, 0.75 mmol, 3.0 eq), and N-(tert-butoxycarbonylamino)-1,5-diaminopentane (105 µl, 0.50 mmol, 2 eq) . The mixture was stirred at room temperature for 5 days, then diluted with 80 ml acetone to produce a precipitate. The solid was collected by filtration to yield 526 mg of crude solid.

The analytical method for analysis was 100/0-25/75%, A/B over 30 minutes (A-0.1% TFA, 5% acetonitrile in water and B-acetonitrile). The UV wavelength used was 235 nm and the flow rate was 2 ml/minute. Analysis was done using a Waters µ bondapak™ C18 column (3.9 X 300 mm, 10 µm, 125 A).

The solid was purified by preparative reverse-phase high performance liquid chromatography (HPLC) on a Waters Prep 2000 system using a Waters Nova-pak® C18 cartridge [3 X (40 X 100 mm), 6 µm, 60 A] with a Waters Nova-pak® C18 guard insert. The solvent system utilized was 0/100-75/25, B/C over 30 minutes (B-acetonitrile and C=0.1% TFA, 5% acetonitrile in water). The UV wavelength used was 235 nm and the flow rate was 50 ml/minute. The titled product was isolated (125 mg, 21% yield) and characterized by FAB-MS: calcd for $C_{96}H_{117}Cl_3N_{12}O_{27}$ 1974.7, found 1976.2 (M+2H).

Example 26:

N^4-(4-(4-CHLOROPHENYL)BENZYL)A82846B, 5-AMINOPENTYLAMIDE, TETRA(TRIFLUOROACETATE) SALT

A mixture/suspension of N^4-(4-(4-chlorophenyl)benzyl) A82846B, 5-(tert-butoxycarbonylamino)pentylamide, tris (trifluoroacetate) salt, 0.125 g, 0.0539 mmol, 1 eq) in 15 ml dichloromethane was treated with trifluoroacetic acid (500 µl, 6.49 mmol, 120.4 eq) at 0°C. The reaction was stirred and allowed to warm to room temperature over 2.25 hours. A residue adhered to the side of the flask and was dissolved by adding methanol. The solvents were removed under vacuum and the residue was azeotroped with toluene (2X) to yield a white solid. The solid was analyzed and purified as above to yield the titled product (77 mg, 61% yield). The material was characterized by FAB-MS: calcd for $C_{91}H_{109}Cl_3N_{12}O_{25}$ 1874.7, found 1877.7 (M+3).

The compounds of Formula I are useful for the treatment of bacterial infections. Therefore, in another embodiment, the present invention is directed to a method for controlling a bacterial infection in a host animal, typically a warm-blooded animal, which comprises administering to the host animal an effective, antibacterial amount of a compound of Formula I. In this embodiment, the compounds of the present invention can be used to control and treat infections due to various bacteria, but especially gram-positive bacteria. In a preferred embodiment, the compounds are used to control and treat infections due to bacteria resistant to existing antibacterials. For example, certain bacteria are resistant to methicillin, and yet others are resistant to vancomycin and/or teicoplanin. Strains of Enterococcus resistant to vancomycin are referred to as "VRE" (vancomycin-resistant Enterococcus); these strains represent a serious problem, especially in nosocomial settings. The present compounds provide a technique for controlling and treating infections due to VRE.

In carrying out this embodiment of the invention, the compounds can be administered by any of the conventional techniques, including the oral route and parenteral routes such as intravenous and intramuscular. The amount of compound to be employed is not critical and will vary depending on the particular compound employed, the route of administration, the severity of the infection, the interval between dosings, and other factors known to those skilled in the art. In general, a dose of from about 0.5 to about 100 mg./kg. will be effective; and in many situations, lesser doses of from about 0.5 to about 50 mg./kg. will be effective. A compound of the present invention can be administered in a single dose, but in the known manner of antibacterial therapy, a compound of the present invention is typically administered repeatedly over a period of time, such as a matter of days or weeks, to ensure control of the bacterial infection.

Also in accordance with known antibacterial therapy, a compound of the present invention is typically formulated for convenient delivery of the requisite dose. Therefore, in another embodiment, the present invention is directed to a pharmaceutical formulation comprising a compound of Formula I, in combination with a pharmaceutically-acceptable diluent or carrier. Such diluents and carriers are well known for both oral and parenteral routes of delivery. In general, a formulation will comprise a compound of the present invention in a concentration of from about 0.1 to about 90% by weight, and often from about 1.0 to about 3%.

The antibacterial efficacy of the present compounds is illustrated in TABLE 2. The minimal inhibitory concentrations (MICs) were determined using a standard broth micro-dilution assay.

TABLE 2

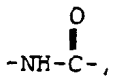
Enterococcus Screen, Minimum Inhibitory Concentrations (MICs)

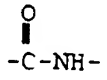
Ex. #	Mean Values of 4-6 Isolates		Selected Individual Pathogens*							
	Resistant	Sensitive	SA 446	SA 489	SA 447	SH105	SH415	SE270	S PN P1	S PY 203
1	1.4	0.13	4	2	1	2	2	0.25	≥0.125	≥0.06
2	1.19	0.041	1	1	0.5	0.125	0.25	≥0.06	≥0.06	≥0.06
3	2.4	0.11	2	4	2	0.5	2	1	≥0.06	≥0.06
4	2	0.082	2	1	0.5	1	2	0.125	≥0.06	≥0.06
5	4	0.22	8	2	2	4	2	4		≥0.06
6	1.7	0.44	4	2	1	1	4	1		≥0.06
7	1.7	0.048	2	1	2	0.5	1	0.5	≥0.06	≥0.06
8	6.7	0.33	2	4	2	4	4	2	≥0.06	≥0.06
9	2	0.082	1	1	1	1	1	0.5	≥0.06	≥0.06
10	0.84	0.14	1	4	2	0.5	4	0.5	≥0.06	≥0.06
11	1	0.11	4	1	1	1	1	1	≥0.06	≥0.06
12	1.7	0.13	2	0.5	1	1	4	2	≥0.06	≥0.06
13	1.4	0.072	1	1	1	2	0.5	1	≥0.06	≥0.06
14	2	0.01	2	1	2	0.5	2	1	≥0.06	≥0.06
15	1.7	0.22	2	2	2	1	2	2	≥0.06	≥0.06
16	16	0.25	0.125	≥0.06	≥0.06	≥0.06	0.125	≥0.06	≥0.06	≥0.06
17	1.4	0.25								
18	0.84	0.19	1	2	1	2	2	1	≥0.06	≥0.06
19	1	0.22	2	2	4	2	4	2	≥0.06	≥0.06
20	11	0.22	0.125	≥0.06	≥0.06	0.125	0.25	≥0.06	≥0.06	≥0.06
21	1.2	0.054	4	2	2	0.5	2	0.5	≥0.06	≥0.06
22	1.68	0.87	32	32	32	8	8	16	0.125	0.125
23	>128	0.44	0.125	≥0.06	0.125	≥0.06	≥0.06	≥0.06	≥0.06	≥0.06
24	>128	0.38	≥0.06	≥0.06	≥0.06	≥0.06	≥0.06	≥0.06	≥0.06	≥0.06
25	2.8	5.0								
26	1.7	0.44		2	1	0.5	2	1	0.25	0.25

* SA 446 = *Staphylococcus aureus* 446
SA 489 = *Staphylococcus aureus* 489
SA 447 = *Staphylococcus aureus* 447
SH 105 = *Staphylococcus haemolyticus* 105
SH 415 = *Staphylococcus haemolyticus* 415
SE 270 = *Staphylococcus epidermis* 270
S PN P1 = *Streptococcus pneumoniae* P1
S PY 203 = *Streptococcus pyogenes* 203

wherein each R^4 independently represents phenyl, cycloalkyl of C_5-C_6, naphthyl, or thienyl, each of which is unsubstituted or is optionally substituted with one or two substituents, each of which is independently alkyl of C_1-C_{10}, haloalkyl of C_1-C_2, haloalkoxy of C_1-C_2, alkoxy of C_1-C_{10}, halo, cyano, or nitro;
and "linker" is:

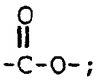
- alkylene of C_1-C_3,
- O-alkylene of C_1-C_6,
- alkylene of C_1-C_6-O-,
- O-,
- N(H or loweralkyl of C_1-C_3)-,
- S-,
- SO-,
- SO_2-,





- CH=CH-,
- C≡C-,
- N=N-,

or



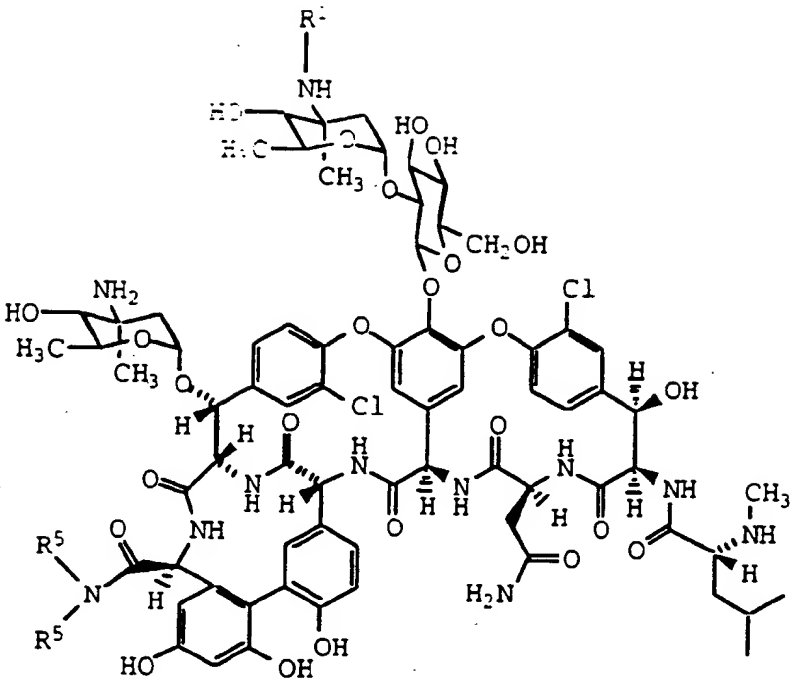
and wherein R^5 is defined as follows:

(1) each R^5 independently represents

hydrogen,
cycloalkyl of C_5-C_6,
cycloalkenyl of C_5-C_6,
phenyl or substituted phenyl bearing from one to three substituents, each of which is independently halo, nitro, loweralkyl of C_1-C_4, cycloalkyl of C_5-C_6, loweralkoxy of C_1-C_4, halologweralkyl of C_1-C_4, or halologweralkoxy of C_1-C_4;
naphthyl,
biphenylyl,
radical of the formula $-R^6-(R^7)_0$, 1, or 2, wherein R^6 is loweralkyl of C_1-C_8 optionally substituted by from one to three substituents, each of which is independently selected from the group consisting of halo, nitro,

Claims

1. A compound of the formula:



I

wherein R^1 is:

hydrogen or $-CH_2R^2$;

wherein R^2 is:

hydrogen,
alkyl of C_1-C_{15},
alkenyl of C_2-C_{15},
alkynyl of C_2-C_{15},
haloalkyl of C_1-C_7,
acenaphthenyl,
2-fluorenyl,
9,10-dihydro-2-phenanthrenyl,
R^3,
alkyl of C_1-C_{11}-R^3,
alkenyl of C_2-C_7-R^3,
alkynyl of C_2-C_7-R^3, or
alkyl of C_1-C_7-O-R^3,

wherein R^3 is a radical of the formula:

$$-R_4-\left[\text{linker}_{(0 \text{ or } 1)}-R^4\right]_{(0 \text{ or } 1)}$$

cyano, loweralkoxy of C_1-C_4, haloloweralkyl of C_1-C_4, and haloloweralkoxy of C_1-C_4; and R^7 is

wherein each R^8 is independently hydrogen or loweralkyl of C_1-C_4 or one R^8 is hydrogen and the other R^8 is tert-butoxycarbonyl, or R^7 is phenyl or substituted phenyl as defined above, or

(2) one R^5 is hydrogen and the other R^5 is (2-furanon-3-yl); or

(3) both R^5s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C_1-C_2, loweralkoxy of C_1-C_2, phenyl, benzyl, or C_1-C_6-alkanoyl; or a salt thereof.

2. A compound of Claim 1 wherein R^1 is $-CH_2R^2$ and R^2=R^3.

3. A compound of either of Claims 1-2 wherein R^1 is 4-phenylbenzyl.

4. A compound of either of Claims 1-2 wherein R^1 is 4-(4-chlorophenyl)benzyl.

5. A pharmaceutical formulation comprising a compound of any of Claims 1-4 in combination with a pharmaceutically-acceptable diluent or carrier.

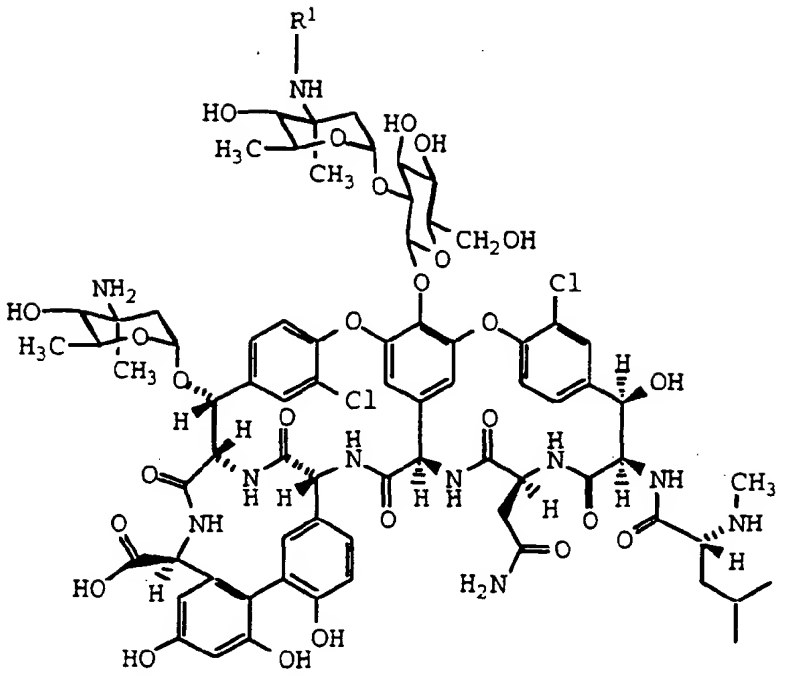
6. A method of treating a bacterial infection in a host comprising the step of administering to the host an effective amount of a compound of any of Claims 1-4.

7. A method of Claim 6 wherein the bacterial infection is attributable to a vancomycin-resistant-enterococcus.

8. A compound of any of Claims 1-4 for use in antibacterial therapy.

9. A compound of any of Claims 1-4 for use in antibacterial therapy against vancomycin-resistant-enterococcus.

10. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of Formula II,



II

wherein R^1 is:

hydrogen or $-CH_2R^2$;

wherein R^2 is:

hydrogen,
alkyl of C_1-C_{15},
alkenyl of C_2-C_{15},
alkynyl of C_2-C_{15},
haloalkyl of C_1-C_7,
acenaphthenyl,
2-fluorenyl,
9,10-dihydro-2-phenanthrenyl,
R^3,
alkyl of C_1-C_{11}-R^3,
alkenyl of C_2-C_7-R^3,
alkynyl of C_2-C_7-R^3, or
alkyl of C_1-C_7-O-R^3;

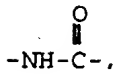
wherein R^3 is a radical of the formula:

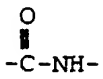
$$-R_4-\left[\text{linker}_{(0 \text{ or } 1)}-R^4\right]_{(0 \text{ or } 1)}$$

wherein each R^4 independently represents phenyl, cycloalkyl of C_5-C_6, naphthyl, or thienyl, each of which is unsubstituted or is optionally substituted with one or two substituents, each of which is independently alkyl of C_1-C_{10}, haloalkyl of C_1-C_2, haloalkoxy of C_1-C_2, alkoxy of C_1-C_{10}, halo, cyano, or nitro;

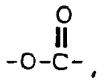
and "linker" is:

- alkylene of C_1-C_3,
- O-alkylene of C_1-C_6,
- alkylene of C_1-C_6-O-,
- O-,
- N(H or loweralkyl of C_1-C_3)-,
- S-,
- SO-,
- SO_2-,

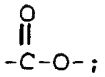




- CH=CH-,
- C≡C-,
- N=N-,



or



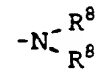
with an amine of the formula

wherein R^5 is defined as follows:

(1) each R^5 independently represents

hydrogen,
cycloalkyl of C_5-C_6,
cycloalkenyl of C_5-C_6,
phenyl or substituted phenyl bearing from one to three substituents, each of which is independently
halo,
nitro,
loweralkyl of C_1-C_4,
cycloalkyl of C_5-C_6,
loweralkoxy of C_1-C_4,
haloloweralkyl of C_1-C_4, or haloloweralkoxy of C_1-C_4,
naphthyl,
biphenylyl,
radical of the formula -R^6-(R^7)0, 1, or 2, wherein R^6 is loweralkyl of C_1-C_8 optionally substituted by from

one to three substituents, each of which is independently selected from the group consisting of halo, nitro, cyano, loweralkoxy of C_1-C_4, halololoweralkyl of C_1-C_4, and halololoweralkoxy of C_1-C_4; and R^7 is



wherein each R^8 is independently hydrogen or loweralkyl of C_1-C_4 or one R^8 is hydrogen and the other R^8 is tert-butoxycarbonyl, or R^7 is phenyl or substituted phenyl as defined above, or

(2) one R^5 is hydrogen and the other R^5 is (2-furanon-3-yl); or
(3) both R^5s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C_1-C_2, loweralkoxy of C_1-C_2, phenyl, benzyl, or C_1-C_6-alkanoyl; and optionally forming a salt thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 30 4495

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,Y	EP 0 667 353 A (LILLY CO ELI) 16 August 1995 * the whole document *	1-10	C07K9/00 A61K38/14
Y	EP 0 435 503 A (LILLY CO ELI) 3 July 1991 * the whole document *	1-10	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	25 August 1997	Deffner, C-A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)